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**Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.**

<b>One MSK Sites</b>
Manhattan
Basking Ridge
Commack
Monmouth
Rockville Centre
Westchester

<b>Baptist Alliance MCI Clinical Trials Sites</b>	<b>PI's Name</b>	<b>Site's Role</b>
Miami Cancer Institute	Miguel Villalona-Calero, MD	Data Collection

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## 1.0 PROTOCOL SUMMARY AND/OR SCHEMA

<b>Study Title :</b>	A Phase II Trial of Albumin- Bound Paclitaxel and Gemcitabine in Patients with Untreated Stage IV or Recurrent Squamous Cell Lung Cancers
<b>Study Objectives:</b>	<p><b><u>Primary Objective:</u></b> To determine the best objective response (partial response and complete response at any time) of albumin-bound paclitaxel and gemcitabine in patients with untreated stage IV or recurrent squamous cell lung cancers</p> <p><b><u>Secondary Objectives:</u></b></p> <ul style="list-style-type: none"> <li>• To evaluate the safety and tolerability of the combination of albumin bound paclitaxel and gemcitabine in this population</li> <li>• To estimate 1 year, 2 year, and median PFS and OS</li> <li>• To correlate genotype with response to therapy</li> </ul>
<b>Patient population:</b>	Untreated stage IV or recurrent squamous cell lung cancer
<b>Number of patients :</b>	17-41 patients
<b>Inclusion Criteria:</b>	<p>All patients must have:</p> <ol style="list-style-type: none"> <li>1. Histologically confirmed squamous cell lung cancer</li> <li>2. Newly diagnosed untreated Stage IV and/or recurrent after adjuvant therapy with metastatic disease</li> <li>3. Patients previously treated with immune checkpoint inhibitor therapy are eligible.</li> <li>4. Measurable disease as per RECIST 1.1</li> <li>5. Greater than 6 months since receiving neo-adjuvant or adjuvant chemotherapy.</li> <li>6. Age <math>\geq 18</math> years</li> <li>7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1</li> <li>8. Women of childbearing potential and sexually active men enrolled in the study must agree to practice effective contraception method during treatment and for three months after completing treatment</li> <li>9. Negative serum or urine <math>\beta</math>-hCG pregnancy test at screening for patients of childbearing potential</li> <li>10. <math>&lt;</math> Grade 2 pre-existing peripheral neuropathy (per CTCAE)</li> <li>11. Marrow and organ function as follows:             <ol style="list-style-type: none"> <li>a. ANC <math>\geq 1500</math> cells/mm<sup>3</sup></li> <li>b. Platelets <math>&gt; 100,000</math> cells/mm<sup>3</sup></li> <li>c. Hemoglobin <math>&gt; 9</math> g/dL</li> <li>d. Creatinine clearance <math>\geq 40</math> mL/min</li> <li>e. Bilirubin <math>\leq 1.5</math> mg/dL</li> <li>f. AST/ALT <math>\leq 2.5 \times</math> upper limit of normal range (ULN), alkaline phosphatase <math>\leq 2.5 \times</math> upper limit of normal,</li> </ol> </li> </ol>

	unless bone metastasis is present in the absence of liver metastasis
<b>Exclusion Criteria:</b>	<p>Patients are to be excluded from the study if they meet any of the following criteria:</p> <ol style="list-style-type: none"> <li>1. Prior treatment with albumin-bound paclitaxel or gemcitabine</li> <li>2. Prior systemic anticancer therapy for metastatic squamous cell lung cancer</li> <li>3. Untreated brain metastasis. Patients with treated brain metastases who are off steroids are eligible</li> <li>4. Peripheral neuropathy greater than grade 1</li> <li>5. Malignancies within the past 5 years other than non-melanoma skin cancer or in situ cervical cancer status post treatment</li> <li>6. Patients with other serious medical illnesses including, ongoing or active infection, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements</li> <li>7. Class III or IV congestive heart failure by New York Heart Association</li> </ol>
<b>Study Drug:</b>	Albumin-bound paclitaxel and gemcitabine
<b>Study Design:</b>	<p>This protocol is a phase II, single institution study of albumin-bound paclitaxel and gemcitabine in patients with stage IV or recurrent squamous cell lung cancer who have not received prior therapy.</p> <p>The study incorporates a Simon-two stage design. The null and desired response rate are selected as 25% and 45%. In stage 1, 17 patients will enter the study. If there are fewer than 6 responses, the study will be terminated early. If 6 or more patients respond, enrollment will be extended to 41 patients. At the end of the study, if 15 or more of the 41 evaluable patients responds, the treatment regimen will be declared worthy of further testing.</p> <p>Patients will be treated as follows: albumin-bound paclitaxel 100mg/m<sup>2</sup> and gemcitabine 1000mg/m<sup>2</sup> on days 1 and 8. Each cycle consists of 21 days. Treatment will continue until disease progression or intolerable side effects. After the 4<sup>th</sup> cycle of therapy, patients will have the option of stopping gemcitabine and proceeding with weekly albumin-bound paclitaxel as maintenance therapy.</p> <p>Toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. Response to therapy will be assessed by interval imaging with CT scan of the chest after every 2 cycles with response evaluated per RECIST 1.1.</p>

<b>Correlative Studies</b>	Molecular testing through the Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT) will be performed at the time of diagnosis or when tissue is available in order to characterize tumor genotype and explore its correlation with response to treatment. These include assessment of <i>FGFR1</i> amplification status, PI3K axis aberrations ( <i>PIK3CA</i> mutations, <i>PTEN</i> mutations, and <i>PTEN</i> loss), <i>DDR2</i> mutations, and exon-capture/next generation sequencing for somatic variations and copy number changes in 279 oncogenes and tumor suppressors.
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## 2.0 OBJECTIVES AND SCIENTIFIC AIMS

**Hypothesis:** Albumin-bound paclitaxel will potentiate gemcitabine activity and will lead to a synergistic increase in response rate and progression free survival.

**Primary Objective:** To determine the best objective response (complete response + partial response at any time before progression, by RECIST) of the combination of albumin-bound paclitaxel and gemcitabine in patients with stage IV or recurrent squamous cell lung cancer

**Secondary Objectives:**

- To evaluate the safety and tolerability of the combination of albumin-bound paclitaxel and gemcitabine in patients with Stage IV squamous cell lung cancers
- To estimate 1 year, 2 year, and median PFS and OS
- To explore the correlation between tumor genotype and response

## 3.0 BACKGROUND AND RATIONALE

### **3.1 SQUAMOUS CELL LUNG CANCER (SQCLC)**

#### **Unmet Therapeutic Needs**

Non-small cell lung cancer remains the leading cause of cancer related mortality in the US and worldwide. Squamous cell lung cancer accounts for approximately 25% of all non-small cell lung cancer cases. In the United States, 55,000 patients are diagnosed with squamous cell lung cancer per year, with approximately half of these patients harboring metastatic disease at diagnosis. Patients with advanced squamous cell lung cancers generally have a poor prognosis with a median survival of 12 months. Furthermore, these patients have fewer therapeutic options than those with other histologies. Pemetrexed, which has greater efficacy in non-squamous NSCLC, is not FDA approved for patients with squamous cell lung cancers.<sup>1</sup> Because of rare cases of life threatening hemoptysis in early phase clinical trials, bevacizumab is similarly not FDA approved for patients with squamous cell lung cancers. Most pressing of all is the current absence of druggable molecular targets in squamous cell lung cancers. For instance, activating mutations in *EGFR* that render lung tumors sensitive to erlotinib and afatinib and *ALK* rearrangements that sensitize to treatment with crizotinib do not occur in SQCLCs.<sup>2</sup> Taken together, there remains a high unmet medical need for new treatment for squamous cell lung cancer.

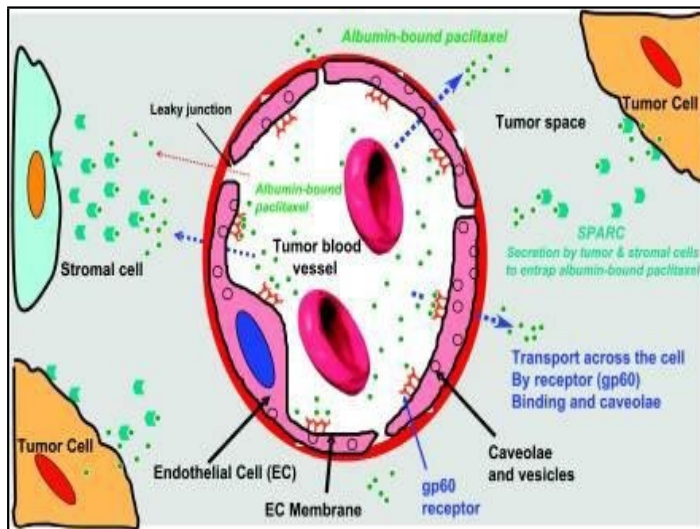
## **Current First Line Treatment for Squamous Cell Lung Cancer**

Platinum based doublet chemotherapy with a third generation therapeutic, most commonly with a taxane or gemcitabine, remains the first line treatment for patients with newly diagnosed Stage IV squamous cell lung cancers. These therapies have similar response rates and median overall survivals. Unfortunately, a large portion of the population cannot tolerate platinum based therapies based on poor performance status and/or history of baseline hearing loss, renal insufficiency, or other comorbid medical conditions such as diabetes and heart failure which precludes them from platinum-based therapy. Although carboplatin is often substituted for cisplatin, it is associated with increased myelosuppression. Development of an effective non-platinum containing chemotherapy regimen with improved response rates are desperately needed for patients with advanced squamous cell lung cancer. Beyond toxicity concerns, no first-line regimen has surmounted the modest activity associated with first-line platinum doublet chemotherapy, which has an overall response rate of only 35% and a median PFS of just 4-6 months. Within this context, existing data suggest that there are chemotherapy agents that exhibit greater efficacy against squamous cell lung cancer tumors as compared to other histologies. Chief among these is albumin-bound paclitaxel and gemcitabine.

### **3.2 ALBUMIN-BOUND PACLITAXEL**

#### **Preclinical Studies:**

Albumin bound paclitaxel was initially developed to avoid toxicities associated with oil-based solvents required to solubilize paclitaxel, such as cremophor EL. Albumin-bound paclitaxel combines non-modified human serum albumin and paclitaxel in a 130nm particle formulation. Preclinical studies suggest that albumin-bound paclitaxel may reach the tumor micro-environment more efficiently than solvent based-paclitaxel and may be preferentially taken up by cancer cells.<sup>3</sup> It is believed that this process occurs via an albumin specific receptor mediated transport process in which albumin binds to gp60 on the endothelial cell wall.<sup>3</sup> This activates caveolin 1 and leads to the formation of caveolae which allow for the transport of the albumin-bound chemotherapeutic complex to the underlying tumor interstitium. SPARC (secreted protein acidic and rich in cysteine) is a matricellular protein up-regulated in several cancers, which binds and entraps albumin, allowing release of the hydrophobic drug to the tumor.<sup>4</sup> Therefore, albumin-bound paclitaxel exploits this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reduce toxic drug in normal tissue.



**Figure 2.1** Mechanisms for the transport and accumulation of albumin-bound paclitaxel in tumors.

Desai, Neil et al. Trans Oncol. 2009 May; 2(2):59-64.

### **Clinical Studies:**

The efficacy and safety of albumin-bound paclitaxel has been tested in several clinical trials in non-small cell lung cancer. In one phase II study, albumin-bound paclitaxel was administered to forty-three patients with untreated non-small cell lung cancer without steroid or antihistamine premedication at a dose of 260mg/m<sup>2</sup> every three weeks.<sup>5</sup> A median of six cycles were administered and 95% of patients were treated without a dose reduction. No severe hypersensitivity reactions were reported. The overall response rate was 16% and median survival was 11 months.

In our Phase I/II study, led and reported by Dr. Naiyer Rizvi (IRB protocol #03-111), patients were treated with albumin-bound paclitaxel on days 1, 8 and 15 of a 28 day cycle.<sup>6</sup> During the Phase I portion, 100mg/m<sup>2</sup> was determined to be the maximum tolerated dose. **The objective response rate was 30% in this untreated population, with a median overall survival of 11 months.** This is comparable to the efficacy of platinum doublet therapy in the first-line setting. It was determined that an infusion rate of two hours as compared to 30 minutes caused less peripheral neuropathy.<sup>7</sup> The median number of cycles administered was four (range, 1 to 14). No hypersensitivity reactions were observed. Notably, 58% were aged ≥ 70, accurately reflecting the percent of elderly patients in the United States with this illness.

A randomized phase III trial of carboplatin plus albumin-bound paclitaxel versus carboplatin plus paclitaxel in untreated stage IV SQCLC patients was associated with a near doubling of the overall response rate from 24% to 41% ( $p < 0.001$ ) in patients with squamous versus non-squamous histology.<sup>8</sup> Furthermore, although the median cumulative taxane dose and average dose intensity were higher for albumin-bound paclitaxel, in general albumin-bound paclitaxel was better tolerated, with lower rates of grade 3 and 4 neuropathy, neutropenia, arthralgia, and myalgia.

The PK of *nab*-paclitaxel in pediatric patients with solid tumors was examined from the ABI-007-PST-001 study. After a single 30-minute IV infusion of *nab*-paclitaxel, dose-normalized peak drug exposure values (C<sub>max</sub>) were comparable across the dose range studied; however, dose-normalized total drug exposure values (AUC) were only comparable across 120 to 240 mg/m<sup>2</sup> with lower dose-normalized AUC<sub>24</sub> and AUC<sub>∞</sub> at the 270 mg/m<sup>2</sup> dose level. These results suggest a less than dose

proportional increased extent of exposure at the highest dose level tested in pediatrics. Mean whole blood CL and volume of distribution at the steady state (Vss) increased from the younger to the older pediatric age groups. In summary, PK in pediatrics is consistent with saturable elimination at higher doses, as well as the deep distribution of paclitaxel that was previously observed in adult patients with advanced or metastatic solid tumors.

### **3.3 GEMCITABINE**

Gemcitabine is an active therapy in squamous cell lung cancer. In a phase III trial of first line therapy in NSCLC randomizing patients to cisplatin plus either gemcitabine or pemetrexed, cisplatin plus gemcitabine was associated with a significantly higher median OS compared to cisplatin plus pemetrexed in patients with squamous cell lung cancer (10.8 v 9.4 months, respectively).<sup>1</sup> It is hypothesized that the short half life of gemcitabine may be a barrier to its antitumor activity in vivo. As such, methods that increase gemcitabine delivery or stability have been proposed to circumvent this problem, specifically with the addition of albumin-bound paclitaxel.

### **3.4 RATIONALE FOR COMBINING ALBUMIN-BOUND PACLITAXEL WITH GEMCITABINE**

#### **Pre clinical studies:**

There is compelling evidence that antitumor synergy exists between gemcitabine and albumin-bound paclitaxel. Frese et al showed that albumin-bound paclitaxel downregulates cytidine deaminase, the primary enzyme that metabolically inactivates gemcitabine, leading to an increase in gemcitabine concentration in a mouse model of pancreatic adenocarcinoma.<sup>9</sup> These data are consistent with mouse xenografts of pancreatic adenocarcinoma where the intra-tumoral gemcitabine concentration was 2.8 times higher when albumin bound paclitaxel was given concurrently.

#### **Clinical studies:**

Based on these data, a series of clinical trials assessing the safety and efficacy of albumin-bound paclitaxel plus gemcitabine were performed. A phase I/II trial of albumin-bound paclitaxel and gemcitabine in patients with previously untreated advanced pancreatic cancer showed that the maximum tolerated dose was 1,000mg/m<sup>2</sup> of gemcitabine plus 125mg/m<sup>2</sup> of albumin-bound paclitaxel given once weekly for 3 weeks every 28 days with a response rate of 48%.<sup>10</sup> A randomized phase III trial of albumin bound paclitaxel plus gemcitabine versus gemcitabine alone in patients with untreated pancreatic adenocarcinomas saw a tripling of the ORR from 7% to 23% in favor of the combination, and a marked increase in progression free survival and overall survival (HR 0.69,  $p<0.001$  and HR 0.72,  $p<0.001$  respectively).<sup>11</sup> This study quickly led to the FDA approval of albumin-bound paclitaxel plus gemcitabine as first-line therapy in patients with untreated stage IV pancreatic cancer in late 2013.

In non-small cell lung cancer, several phase II trials of weekly paclitaxel plus gemcitabine as first line treatment showed that this drug combination is an active and well tolerated regimen for the treatment of advanced NSCLC, with an overall response rate of 23%-55%, median survival of 4.9-11.9 months and 1 year survival rate of 26-53%.<sup>12-19</sup>

First author (ref.)	No. of patients		Regimen and schedule	Response rate (%)	Survival median	One-year (%)
Belani et al. [12]	50	Arm A	P 200 mg/ m <sup>2</sup> day 1 q3w	28.2	7.5	34
			G 1 g/ m <sup>2</sup> days 1, 8 q3w			
	50	Arm B	P 100 mg/ m <sup>2</sup> days 1, 8 q 3w	26.8	9.6	42
			G 1 g/ m <sup>2</sup> days 1, 8 q3w			
Bhatia et al. [13]	39		P 110 mg/ m <sup>2</sup> days 1, 8, 15 q 4w	38.2	4.9	26
			G 1 g/ m <sup>2</sup> days 1, 8, 15 q4w			
De Pas et al. [14]	54		P 100 mg/ m <sup>2</sup> days 1, 8, 15, 22 q 4w	46	9.6	53
			G 1 g/ m <sup>2</sup> days 1, 8, 15, 22 q4w			
Akerley et al. [15]	39		P 85 mg/ m <sup>2</sup> days 1, 8, 15, 22, 29, 36 q 8w	23.1	7.5	32
			G 1 g/ m <sup>2</sup> days 1, 8, 15, 22, 29, 36 q8w			
Gillenwater et al. [16]	39		P 100 mg/ m <sup>2</sup> days 1, 8, 15, 21 q 4w	35	4.9	35
			G 1 g/ m <sup>2</sup> days 1, 8, 15, 21 q4w			
Kosmidis et al. [17]	225		P 200 mg/ m <sup>2</sup> day 1 q 3w	31	9.3	42
			G 1 g/ m <sup>2</sup> days 1, 8, q3w			
Treat et al. [18]	312		P 200 mg/ m <sup>2</sup> day 1 q 3w	43.6	8.4	33
			G 1 g/ m <sup>2</sup> days 1, 8, q3w			
Mori, et al. [19]	40		P 100 mg/ m <sup>2</sup> days 1, 8, q 3w	55	11.9	47.5
			G 1 g/ m <sup>2</sup> days 1, 8 q3w			

### **3.5 GOAL OF STUDY:**

In light of the greater single-agent activities of both albumin-bound paclitaxel and gemcitabine in squamous cell lung cancer versus non-squamous NSCLCs, we hypothesize that the same synergistic increase in efficacy seen with albumin-bound paclitaxel and gemcitabine in pancreatic adenocarcinoma will also be seen in squamous cell lung cancer, opening a new avenue of therapy to those who are, at a minimum, ineligible for treatment with platinum chemotherapy and which, at most, may supplant platinum chemotherapy as a new standard of care for these patients.

## **4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION**

### **4.1 Design**

This is an open label, single institution phase II trial of albumin-bound paclitaxel and gemcitabine in patients with untreated stage IV or recurrent squamous cell lung cancer. A Simon two-stage design will be applied. The primary endpoint is best objective response.

A maximum of 17 patients will be enrolled in the first stage of the study. If there are fewer than 6 responses, the study will be terminated early. If 6 or more patients respond, enrollment will be extended to 41 patients. At the end of stage 2, if 15 or more patients respond, the treatment regimen will be declared worthy of further testing.

## **4.2 Intervention**

Patients with stage IV or recurrent squamous cell lung cancer who have received no prior treatment for metastatic disease will be enrolled in this trial. During each 21-day cycle, albumin-bound paclitaxel at 100 mg/m<sup>2</sup> over 120 minutes and gemcitabine at 1000mg/m<sup>2</sup> over 30 minutes will be given intravenously on days 1 and 8 of each 21 day cycle. Treatment will continue until disease progression or intolerable side effects. After the 4<sup>th</sup> cycle of treatment, patients will have the option of discontinuing gemcitabine and proceeding with weekly albumin-bound paclitaxel as maintenance therapy.

Patients will be evaluated before each treatment on day 1 and 8. Safety evaluations will consist of medical history, physical examination, vital signs, and blood work during each day of treatment. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. This treatment regimen will be continued until documentation of disease progression, unacceptable toxicity, or patient refusal.

To assess response, patients will have a CT scan of the chest and other sites of disease after every 2 cycles.

## **4.3 Correlative Studies**

Molecular testing through Dr. Paik's Squamous Cell Lung Cancer Mutation Analysis Program will be performed at the time of diagnosis or when tissue is available in order to molecularly characterize patients for associations with response. These include assessment of *FGFR1* amplification status, PI3K axis aberrations (*PIK3CA* mutations, *PTEN* mutations, and *PTEN* loss), *DDR2* mutations, and exon-capture/next generation sequencing for somatic variations and copy number changes in 279 oncogenes and tumor suppressors.

## **5.0 THERAPEUTIC/DIAGNOSTIC AGENTS**

### **5.1. Albumin-bound paclitaxel (ABI-007, Abraxane ®):**

Albumin-bound paclitaxel is a Cremophor EL-free form of paclitaxel with a mean particle size of approximately 130 nanometers. Each 50-mL single-use vial contains 100 mg of paclitaxel, and approximately 900 mg of human albumin. Albumin-bound paclitaxel is supplied as a white to yellow sterile lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection USP.

#### **5.1.1. Dosing and Administration:**

Albumin-bound paclitaxel will be administered intravenously at 100mg/m<sup>2</sup> on days 1 and 8 of a 21-day cycle together with gemcitabine. After the 4<sup>th</sup> cycle of therapy, patients will have to option to receive albumin-bound paclitaxel alone as maintenance therapy at 100mg/m<sup>2</sup> on days 1 and 8 of a 21-day cycle. The drug will be given over 120 minutes <sup>6, 7</sup>. NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of albumin-bound paclitaxel. In any event, filters of pore-size less than 15 micrometers must not be used.

#### **5.1.2. Supply and Packaging:**

Albumin-bound paclitaxel will be supplied by Celgene, in single-use vials. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg of human albumin (HA) as a stabilizer. Each vial will be labeled according to regulatory requirements for labeling of investigational products. The study medication will be dispensed by the MSKCC pharmacy.

#### **5.1.3. Storage and Stability:**

Unreconstituted albumin-bound paclitaxel should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its carton and retained in the original package to protect from bright light. Unopened vials of albumin-bound paclitaxel are stable until the date indicated on the package when stored at the above temperatures in the original package. Reconstituted albumin-bound paclitaxel should be used immediately. If not used immediately, the vial of reconstituted albumin-bound paclitaxel must be protected from bright light, placed in its carton and refrigerated at 2° to 8°C (38° to 46°F) for a maximum of 24 hours. Any unused portion of the reconstituted suspension should be discarded. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

#### **5.1.4. Reconstitution and Use of Albumin-bound paclitaxel**

Albumin-bound paclitaxel will be reconstituted by appropriate study personnel and administered to the patient in the study site setting per institutional pharmacy guidelines.

#### **5.1.5. Drug Distribution, Return and Destruction**

##### *Drug Distribution*

Albumin-bound paclitaxel will be distributed by Celgene. No supplies will be shipped until regulatory approval has been obtained. Investigational sites will be supplied with albumin-bound paclitaxel upon identification and screening of a potential trial subject.

Upon identification of a potential subject, the Drug Request Form must be completed and faxed to Celgene. At least 5 working days should be allowed for drug shipment. There are no shipments on Fridays or holidays.

For re-supply of drug, please complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779.

### *Drug Return/Destruction*

Partially used and completely used vials should be discarded according to institutional guidelines, and their disposition should be recorded on an investigational drug accountability form. Drug can be destroyed on site if proper accountability of the destruction is maintained (number of vials, expiration date, lot number, etc.) as well as documentation that the drug was destroyed according to the institution's SOP. Celgene will need to obtain copies of the destruction and a memo stating what was destroyed (lot number and quantity) as well as a copy of the institution's destruction SOP.

The MSKCC pharmacy will keep accountability of the lot and quantity of drug returned. This will be reconciled once the study is fully closed.

### **5.2. Gemcitabine (Gemzar<sup>®</sup>, Eli Lilly)**

Gemcitabine (Gemzar<sup>®</sup>, Eli Lilly) is a commercially available medication with a complete description of the drug, its clinical pharmacology, contraindications, warnings, precautions and adverse reactions available in the package insert. Gemcitabine will be administered intravenously at 1000mg/m<sup>2</sup> on days 1 and 8 of a 21-day cycle. The drug will be given per standard institutional procedures.

## **6.0 CRITERIA FOR SUBJECT ELIGIBILITY**

### **6.1 Subject Inclusion Criteria**

- Histologically confirmed squamous cell lung cancer
- Newly diagnosed untreated Stage IV and/or recurrent after adjuvant therapy with metastatic disease
- Patients previously treated with immune checkpoint inhibitor therapy are eligible
- Measurable disease as per RECIST 1.1
- Greater than 6 months since receiving neo-adjuvant or adjuvant chemotherapy.
- Age  $\geq$  18 years
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
- Women of childbearing potential and sexually active men enrolled in the study must agree to practice effective contraception method during treatment and for three months after completing treatment
- Negative serum or urine  $\beta$ -hCG pregnancy test at screening for patients of childbearing potential
- $<$  Grade 2 pre-existing peripheral neuropathy (per CTCAE)
- Marrow and organ function as follows:
  - ANC  $\geq$  1500 cells/mm<sup>3</sup>
  - Platelets  $>$  100,000 cells/mm<sup>3</sup>
  - Hemoglobin  $>$  9g/dL

Creatinine clearance  $\geq 40$  mL/min

Bilirubin  $\leq 1.5$  mg/dL

AST/ALT  $\leq 2.5 \times$  upper limit of normal range (ULN), alkaline phosphatase  $\leq 2.5 \times$  upper limit of normal, unless bone metastasis is present in the absence of liver metastasis

## 6.2 Subject Exclusion Criteria

- Prior treatment with albumin-bound paclitaxel or gemcitabine
- Prior systemic anticancer therapy for metastatic squamous cell lung cancer
- Untreated brain metastasis. Patients with treated brain metastases who are off steroids are eligible
- Peripheral neuropathy greater than grade 1
- Malignancies within the past 5 years other than non-melanoma skin cancer or in situ cervical cancer status post treatment
- Patients with other serious medical illnesses including, ongoing or active infection, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements
- Class III or IV congestive heart failure by New York Heart Association

## 7.0 RECRUITMENT PLAN

All patients recruited will be under the care of attending medical oncologists on the Thoracic Oncology Service and Regional Networks at MSKCC. Patients will be accrued to this study without regard for gender or minority status.

## 8.0 PRETREATMENT EVALUATION

**The following test must be ordered before patient enrollment:**

- Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT)

**The following tests must be completed within 28 days of patient enrollment:**

- Complete medical history
- Complete physical examination
- Determination of performance status on the Karnofsky scale
- CT scan of the chest and other relevant disease sites
- MRI brain with gadolinium or CT head with contrast

**The following tests must be completed within 14 days of patient enrollment:**

- CBC with differential
- Comprehensive metabolic panel

**The following test must be completed within 7 days of patient enrollment:**

- Women of childbearing potential must have a negative pregnancy test

## 9.0 TREATMENT/INTERVENTION PLAN

Patients will be treated with albumin-bound paclitaxel and gemcitabine as follows in an every 21-day cycle until disease progression or the decision is made to begin maintenance therapy:

Days 1 and 8: Albumin-bound paclitaxel ( $100 \text{ mg/m}^2$  over 120 minutes) + Gemcitabine ( $1000 \text{ mg/m}^2$  over 30 minutes)

After the 4<sup>th</sup> cycle of therapy, patients will have the option to begin maintenance therapy in an every 21-day cycle as follows:

Days 1 and 8: Albumin-bound paclitaxel ( $100 \text{ mg/m}^2$  over 120 minutes)

Dose reductions and omissions will be allowed for toxicities according to guidelines specified in Section 11.0.

### Albumin-bound paclitaxel pre-medication

Patients do not require premedication prior to albumin-bound paclitaxel administration, as hypersensitivity reactions are not expected. Initial antiemetic prophylaxis is recommended due to administration of gemcitabine following albumin-bound paclitaxel treatment. If a hypersensitivity reaction occurs, the infusion should be stopped and not restarted. At the investigator's discretion, treatment may continue on subsequent cycles using the premedication regimen the institution typically uses for Taxol if felt to be in the patient's best interest.

### Gemcitabine pre-medication

Initial antiemetic prophylaxis is recommended with dexamethasone 8 IV prior to administration of gemcitabine. If a patient experiences nausea and/ or vomiting following the first dose, then institutional guidelines should be followed for breakthrough antiemetic management.

## 10.0 EVALUATION DURING TREATMENT/INTERVENTION

Patients enrolled in this study will require an office visit prior to each dose of chemotherapy. They will be evaluated clinically and with standard laboratory tests on days 1 and 8 of each 21-day cycle. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and laboratory measurements during each day of treatment (see **Table 10.1**).

Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

A CBC and comprehensive metabolic panel will be drawn and checked at each visit with dose adjustments made according to Section 11.0 of the protocol. Tests should be performed within 7 days prior to dosing. The results of the comprehensive metabolic panel must be reviewed prior to chemotherapy administration, and appropriate dose adjustments made according to Section 11.0 of the protocol.

To assess response, patients will have a CT scan of the chest and other clinically relevant sites after every 2 cycles.

<b>Table 10.1 Study Flow Chart</b>										
		Cycle 1			Cycle 2+			Maintenance therapy		End of Study
Assessment	Baseline	Day 1	Day 8	Week 3	Day 1	Day 8	Week 3	Day 1	Day 8	Within 30 days of last treatment
Medical History	X <sup>c</sup>	X	X		X	X		X	X	X
Physical Exam	X <sup>c</sup>	X	X		X	X		X	X	X
Performance status	X <sup>c</sup>	X	X		X	X		X	X	X
CBC <sup>a</sup>	X <sup>d</sup>	X <sup>f</sup>	X <sup>f</sup>		X <sup>f</sup>	X <sup>f</sup>		X <sup>f</sup>	X <sup>f</sup>	X
CMP <sup>b</sup>	X <sup>d</sup>	X <sup>f</sup>	X <sup>f</sup>		X <sup>f</sup>	X <sup>f</sup>		X <sup>f</sup>	X <sup>f</sup>	X
Pregnancy test for women of childbearing potential	X <sup>e</sup>									
CT chest and other relevant disease sites	X <sup>c</sup>						X <sup>g</sup>		X <sup>g</sup>	
Brain MRI gadolinium or CT contrast	X <sup>c</sup>									
Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT)	X <sup>h</sup>									
<b>Treatment:</b> Albumin		X <sup>i</sup>	X <sup>i</sup>		X <sup>i</sup>	X <sup>i</sup>		X <sup>i</sup>	X <sup>i</sup>	

bound paclitaxel										
Gemcitabine		X <sup>d</sup>	X <sup>d</sup>		X <sup>d</sup>	X <sup>d</sup>				

<sup>a</sup> Complete blood count, with platelet count and differential.

<sup>b</sup> Comprehensive metabolic panel.

<sup>c</sup> Within 28 days prior to starting treatment.

<sup>d</sup> Within 14 days prior to starting treatment.

<sup>e</sup> Pregnancy testing is mandatory for all women of childbearing potential. Must be done within 7 days prior to starting treatment.

<sup>f</sup> May be obtained within 7 days if same-day blood work not available.

<sup>g</sup> CT scan of chest and other relevant disease sites will be performed during week 3 after every 2 cycles. (+/- 7 day window)

<sup>h</sup> Molecular testing through MSK-IMPACT will be performed prior to study initiation

<sup>i</sup> There must be at least 7 days in between treatments. The treatment window is (+/- 7 days)

## 11.0 TOXICITIES/SIDE EFFECTS

Toxicity grading will be performed in accordance with NCI CTCAE, version 4.0.

### 11.1 Known Potential Side Effects

#### *Albumin-bound paclitaxel (Abraxane®)*

Albumin-bound paclitaxel is not formulated in cremophor and thus the risk of hypersensitivity reactions is much less than that of Taxol. The major risks of albumin-bound paclitaxel have been assessed in clinical trials in patients with a variety of malignancies. The most common toxicities reported following albumin-bound paclitaxel administration are:

- Hematologic: Grade 4 neutropenia was reported and typically resolved in <7 days and did not require colony stimulating factor support. Anemia, febrile neutropenia, leukopenia, lymphopenia, pancytopenia and thrombocytopenia were common occurrences. Thrombotic thrombocytopenic purpura occurred infrequently.
- Nervous System Disorders: Grade 3 peripheral neuropathy was reported and typically improved to Grade 1 or 2 within 21 days of interrupting the albumin-bound paclitaxel dose. Following resolution of the peripheral neuropathy to acceptable levels, clinicians were able to restart albumin-bound paclitaxel dosing at a lower dose level. Ataxia, dizziness, dysgeusia and headache were commonly observed occurrences. Facial paralysis was an uncommon occurrence.
- Gastrointestinal: Nausea, vomiting, mucositis, anorexia, weight loss, constipation, hepatotoxicity, and diarrhea were seen, typically at Grade 1 or 2 levels. This AE responded well to standard anti-emetic regimens. Mucositis was reported typically Grade 1 or 2. It was not dose-limiting. Abdominal pain, Colitis, dry mouth, dyspepsia, dysphagia, intestinal obstruction and stomatitis were also common occurrences.

- Musculoskeletal and Connective Tissue Disorders: Myalgia, arthralgia, and fluid overload were reported and typically were Grade 1 or 2; these were responsive to standard acetaminophen-containing medication. Muscular pain and weakness were commonly observed occurrences.
- Alopecia: Alopecia was reported by most patients and was similar to that seen with Taxol.
- Infection: Albumin bound paclitaxel contains albumin derived from human blood, which has a theoretical risk of viral transmission. Lower respiratory tract infection including bronchitis, candida infection, folliculitis, nail infection, pneumonia, sepsis, upper respiratory tract infection, and urinary tract infection were common occurrences. Injection site infection and neutropenic sepsis were infrequent occurrences.
- Fetal harm: fetal harm may occur when administered to pregnant women. Women of childbearing potential need to avoid becoming pregnant while on study. Men should be advised to not father a child while on study.
- Respiratory, Thoracic and Mediastinal Disorders: Cough, dyspnea, epistaxis, hemoptysis, nasal congestion, oropharyngeal pain, pleural effusion, pneumonitis and pulmonary embolism were commonly observed occurrences. Dry throat and nasal dryness were uncommonly observed occurrences.
- Cardiac: cardiac failure congestive, palpitations and tachycardia were common occurrences. Arrhythmia, cardiac arrest, left ventricular dysfunction, sinus bradycardia and supraventricular tachycardia are uncommon occurrences. Atrioventricular block occurred at rare frequencies.
- Eye: increased lacrimation and visual impairment were common occurrences. Conjunctivitis, cystoid macular edema, keratitis, and maculopathy were uncommon occurrences.
- General Disorders and Administration Site Conditions: Asthenia, chest pain, chills, fatigue, infusion site reactions, mucosal inflammation, edema and pyrexia were common occurrences. Lethargy and malaise were occasional, uncommon occurrences.
- Hepatobiliary Disorders: cholangitis and hyperbilirubinemia were common occurrences.
- Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and blood creatinine increased were commonly observed occurrences.
- Metabolism and Nutrition Disorders: Decreased appetite, dehydration, hypokalemia were commonly observed occurrences. Fluid retention was uncommonly observed.
- Psychiatric Disorders: anxiety, depression and insomnia were commonly observed occurrences.
- Skin and Subcutaneous Tissue Disorders: alopecia, dry skin, erythema, nail disorder including onycholysis and discoloration, palmar-plantar erythrodysesthesia syndrome, pruritis and rash including generalized are commonly observed occurrences. Dermatitis allergic and erythema multiforme were uncommonly observed occurrences.
- Vascular Disorders: deep vein thrombosis, flushing, hypertension, hypotension and lymphedema were commonly observed occurrences.

### ***Gemcitabine (Gemzar®)***

The most common toxicities reported for gemcitabine are:

- Hematologic: Myelosuppression is the dose-limiting toxicity with gemcitabine, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Patients should be monitored for myelosuppression during gemcitabine therapy and dosage modified or suspended according to the degree of hematologic toxicity
- Gastrointestinal: Nausea and vomiting are commonly reported but were usually of mild to moderate severity. Diarrhea and stomatitis can also be seen
- Hepatic: In clinical trials, gemcitabine was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to gemcitabine or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine.
- Renal: In clinical trials, mild proteinuria and hematuria were commonly reported. Hemolytic Uremic Syndrome (HUS) has been reported rarely (0.25%) with the use of gemcitabine. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.
- Fever: The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that gemcitabine may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.
- Rash: Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.
- Pulmonary: In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with gemcitabine therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of gemcitabine. The etiology of these effects is unknown. If such effects develop, gemcitabine should be discontinued. Early use of supportive care measures may help ameliorate these conditions.
- Edema: Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.
- Flu-like Symptoms: "Flu syndrome" was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.
- Infection: Infections were reported for 16% of patients. Sepsis was rarely reported.
- Alopecia: Hair loss, usually minimal, was reported by 15% of patients.
- Neurotoxicity: There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

## **11.2 Dose Modification Schedule**

Toxicities will be graded using the NCI CTCAE Version 4.0 and dose modifications of the study drugs will be made for hematologic and other toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Patients experiencing study drug related toxicities that require a delay in scheduled albumin-bound paclitaxel and gemcitabine dosing for >21 days will be discontinued from further participation in this study.

**Table 11.1 Dose Modification for Albumin-bound Paclitaxel**

Dose Level	Albumin-bound Paclitaxel (Abraxane <sup>®</sup> )
0	100 mg/m <sup>2</sup>
-1	75 mg/m <sup>2</sup>
-2	50 mg/m <sup>2</sup>
If additional dose reduction required	Discontinue

**Table 11.2 Dose Modification for Gemcitabine**

Dose Level	Gemcitabine (Gemzar <sup>®</sup> )
0	1000 mg/m <sup>2</sup>
-1	800 mg/m <sup>2</sup>
-2	600 mg/m <sup>2</sup>
If additional dose reduction required	Discontinue

### **11.2.1 HEMATOLOGIC TOXICITY:**

A CBC will be obtained prior to each treatment. The following parameters should be observed:

Albumin-bound paclitaxel and gemcitabine dosing should not be administered at the start of each cycle until the absolute neutrophil count returns to  $\geq 1.5 \times 10^9$  cells/L and the platelet count returns to  $> 100 \times 10^9$  cells/L.

For each subsequent dose of albumin-bound paclitaxel and gemcitabine within a cycle, patients must have an ANC  $\geq 1.0 \times 10^9$  cells/L and platelets  $> 75 \times 10^9$  cells/L. If the ANC and platelets are not adequate for treatment, the following dose adjustments will be made (See **Table 11.3**).

**Table 11.3: Dose Modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle**

Cycle Day	ANC (cells/mm <sup>3</sup> )		Platelet count (cells/mm <sup>3</sup> )	Albumin-bound paclitaxel / Gemcitabine
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<b>Day 1</b>	<1500	OR	<100,000	Delay dose for 1 week intervals
<b>Day 8</b>	<1000	OR	<75,000	Reduce 1 dose level + G-CSF (treat on time) or delay dose for 1 week +/- G-CSF (ie. Day 8 retry) or withhold Day 8 dose +/- G-CSF and re-evaluate for Day 15 treatment.
<b>Febrile Neutropenia</b>				
<b>Any Day</b>				Hold doses. Upon resuming dosing decrease to next lower level and do not re-escalate through the rest of treatment.

<sup>A</sup>:G-CSF is optional if patient only with thrombocytopenia. If patient does not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued. G-CSF should be given 24 hours after chemotherapy and held 48 hours prior to the next dose

### **11.2.2 NON-HEMATOLOGIC TOXICITY:**

<b>Table 11.4: Dose Modifications for Non-Hematologic Toxicities</b>		
<b>Adverse Drug Reaction</b>	<b>Albumin-bound paclitaxel</b>	<b>Gemcitabine</b>
<b>Peripheral Neuropathy:</b> Grade 3 or 4	Withhold until neuropathy improved to $\leq$ Grade 1; resume at next lower dose level	Continue. No Dose Reduction
<b>Cutaneous Toxicity:</b> Grade 2 or 3	Reduce to next lower dose level for both drugs	
<b>Gastrointestinal Toxicity:</b> Grade 3 mucositis or diarrhea	Withhold both drugs until improves to $\leq$ Grade 1, then resume both drugs at next lower dose level	
<b>Other Non-Hematologic Toxicities:</b> Grade $\geq$ 3	Withhold both drugs until improves to $\leq$ Grade 1. Consider dose reduction at resumption of one or both drugs per investigator judgment.	
<b>Other Non-Hematologic Toxicities:</b> Grade < 3	If considering dose modification for non-hematologic toxicities grade < 3, must discuss with PI for approval	

The decision regarding which drug to modify will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the physician/investigator.

### **PERIPHERAL NEUROPATHY**

Treatment with albumin bound paclitaxel should be withheld in patients who experience  $\geq$ Grade 3 peripheral neuropathy. Gemcitabine administration can continue during this period. Albumin bound paclitaxel may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to  $\leq$ Grade 1. The time to resolution to Grade  $\leq 1$  should be the adverse event duration used for adverse event reporting. Patients experiencing peripheral neuropathy that requires a delay in scheduled albumin bound paclitaxel dosing for over 21 days will discontinue study treatment.

#### CUTANEOUS TOXICITY

Patients who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level for both drugs. If the patient continues to experience these reactions, despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 cutaneous toxicity should have treatment discontinued.

#### GASTROINTESTINAL TOXICITY

If Grade 3 mucositis or diarrhea occurs, study drugs should be withheld until resolution to  $\leq$ Grade 1, then reinstituted at the next lower dose levels. Patients who develop Grade 4 mucositis or diarrhea should have treatment discontinued.

#### COLONY STIMULATING FACTOR ADMINISTRATION

Table 11.3 provides a guideline for the use of G-CSF or pegfilgrastim and for implementing dose reductions for treatment-related hematologic toxicity. Colony stimulating factors should be given according to institutional guidelines for treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC  $<1000$  cells/uL.

#### HYPERSENSITIVITY REACTIONS:

Hypersensitivity reactions are not expected with either albumin bound paclitaxel or gemcitabine. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. Premedication may be needed in patients who have had prior hypersensitivity reactions to albumin bound paclitaxel. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who develop a severe hypersensitivity reaction to albumin bound paclitaxel should not be re-challenged.

#### ADMINISTRATION OF STUDY DRUG TO PATIENTS WITH ABNORMAL HEPATIC FUNCTION:

Albumin-bound paclitaxel and gemcitabine should only be administered if hepatic function is within the parameters established in the eligibility criteria. Significant hepatic toxicity from taxanes or gemcitabine may occur but is not common. For this reason, hepatic dysfunction that occurs while the patient is on study should prompt evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications.

#### INTERSTITIAL PNEUMONITIS:

Pneumonitis has been reported to occur in 4% of patients who have received the combination of albumin-bound paclitaxel and gemcitabine. Monitor patients for signs and symptoms of pneumonitis and interrupt albumin bound paclitaxel and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and making the diagnosis of pneumonitis, treatment with

gemcitabine should be permanently discontinued and corticosteroids with appropriate ventilation and oxygen support when required should be promptly initiated. If the pneumonitis resolves to grade  $\leq 1$  within 28 days and was grade  $\leq 3$ , the investigator can consider resuming albumin bound paclitaxel as a single agent at a -1 dose level. If pneumonitis recurs, albumin bound paclitaxel should be permanently discontinued.

#### **DISCONTINUATION FROM STUDY:**

After the doses of both albumin-bound paclitaxel and gemcitabine have been reduced twice for an adverse event, the patient will be discontinued from the study.

### **11.3 RULES FOR DOSE OMISSIONS AND MODIFIED SCHEDULES:**

**Day 1 dose held:** If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient.

**Day 8 dose held:** Patients who have therapy held on Day 8 can have a re-attempt at treatment 1 week later. If treatment is held again, the next treatment will be considered Day 1 of a new cycle.

### **11.4 CONCOMITANT MEDICATIONS:**

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Administration of other chemotherapy, immunotherapy, or anti-tumor hormonal therapy during the study is not allowed. Irradiation is not allowed during the study except for symptomatic non-target lesions. All concomitant treatments, including blood and blood products, must be reported on the case report form.

Since albumin-bound paclitaxel is a formulation containing paclitaxel, the potential drug-drug interactions precautions contained in the Taxol<sup>®</sup> package insert will be applied to this study (see Taxol<sup>®</sup> package insert). Specifically, the metabolism of Taxol is catalyzed by cytochrome P450 isozymes CYP2C8 and CYP3A4. Caution is recommended when administering Taxol<sup>®</sup> concomitantly with inducers (e.g.: rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) or inhibitors (ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, and protease inhibitors including ritonavir, saquinavir, indinavir, and nelfinavir) of the cytochrome P450 isozymes CYP2C8 and CYP3A4. Similarly, herbal preparations, and/or dietary supplements known to influence the expression of CYP3A (e.g., St. John's wort, garlic supplements, grapefruit juice) and/or CYP2C8 should be used with caution (see [www.drug-interactions.com](http://www.drug-interactions.com) for a regularly updated list of drug interactions with cytochrome P450 isozymes).

## **12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT**

The Response Evaluation Criteria in Solid Tumors Group 1.1 (RECIST 1.1) will be used to evaluate the response to treatment. The same method and the same technique (i.e. with or without contrast) should be used to characterize each identified and reported lesion at baseline and after every 6 weeks +/- 1 week while on study. If an appropriate imaging study is done early for any reason (i.e. hospitalization), it can be used for disease assessment and the subsequent set of imaging scans may be completed 6 weeks (+/- 1 week) from the date of that assessment. A designated radiologist/physician will be responsible for interpretation of the study imaging according to RECIST v1.1.

A CT scan of the chest or CT chest (+/- abdomen/pelvis depending on sites of disease) with or without contrast will be performed to demonstrate all known areas of measurable disease. The baseline study will occur no more than 4 weeks prior to first study drug administration. An alternative imaging test, including MRI, can be used in patients with contraindications to radiographic contrast media used in CT scans. All patients must have at least one measurable disease lesion by CT or MRI.

Confirmation of an objective response will occur with repeat imaging  $\geq 4$  weeks after the initial response scan.

## 12.1 DISEASE PARAMETERS

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $>20$  mm with conventional techniques (CT, MRI, x-ray) or as  $>10$  mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter  $<20$  mm with conventional techniques or  $<10$  mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions: All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of best overall response: The best overall response is the best response recorded from the start of treatment until disease progression, as defined in **Table 12.1** (See below).

Evaluable for objective response:

Patients evaluable for response are defined as those who complete at least the first planned CT scan after the 2<sup>nd</sup> cycle of therapy.

Progression free survival (PFS): is defined as the duration of time from first treatment to time of progression or death, whichever occurs first.

Overall survival (OS): is defined as the duration of time from first treatment to time of death.

Definitions of response in target and non-target lesions are described in **Table 12.1** and **Table 12.2** below. **Table 12.3** provides overall responses for all possible combinations of tumor responses in target and non-target lesions.

**Table 12.1: Evaluation of target lesions**

Complete Response (CR target lesions):	Disappearance of all
Partial response (PR):	At least a 30% decrease in the sum of the diameters of the target lesions
Progressive disease (PD):	At least a 20% increase in the sum of the diameter of the target lesions or the appearance of one or more new lesions
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

**Table 12.2: Evaluation of non-target lesions**

Complete Response (CR):	Disappearance of all non-target lesions
Incomplete response/Stable disease (SD):	Persistence of one or more non-target lesions
Progressive disease (PD):	Appearance of one or more new lesion and/or unequivocal progression of existing non-target lesion

**Table 12.3: Combination of Responses**

Target Lesions	Non-target lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or NO	PD
Any	PD	Yes or NO	PD
Any	Any	Yes	PD

### 13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time. Patients who discontinue early should return within 30 days of the last dose for a follow up evaluation. Patients who withdraw from the study for reasons other than disease progression without completing a full treatment cycle will be replaced.

Patients will be withdrawn from the study should they experience any of the following:

- Grade 4 adverse event recurs after the dose of both albumin-bound paclitaxel and gemcitabine have been reduced twice
- Disease progression (as defined by RECIST 1.1)
- Change in patient eligibility for the protocol, as designed in the section on Criteria for Patient/Subject Eligibility (i.e: change in diagnosis)
- Investigator's decision based on patient's best interest
- Withdrawal of consent
- Lost to follow up
- Severe, unexpected toxicities/side effects
- Non-compliance with the defined treatment plan
- Death

## **14.0 BIOSTATISTICS**

### **14.1. Primary Objectives**

#### **14.1.1. Objective Overall Response Rates**

The primary efficacy endpoint of the study is the best objective response (BOR) rate, defined as the proportion of patients with complete or partial responses based on RECIST 1.1, at any time prior to disease progression, out of all evaluable patients. A response needs to be confirmed 28 days after it was initially observed.

The trial is designed using a Simon optimal two-stage design. A BOR rate less than 25% is considered not promising (null hypothesis), a BOR rate >45% is promising (alternative hypothesis), and the probabilities of a one-sided Type I error (falsely accepting a non-promising therapy) and Type II error (falsely rejecting a promising therapy) are set to 0.05 and 0.2, respectively. In the first stage of this design, 17 patients will be treated. If fewer than 6 patients have a response, then the study will be terminated and declared negative. If 6 or more patients have a response, then an additional 24 patients will be accrued to the second stage. At the end of the study, the regimen will be considered worthy of further investigation if 15 or more responses are observed among the 41 patients treated. With this design, the probability of early termination under the null hypothesis is 77%, and the expected sample size is 23.

We expect to accrue 2 patients/month to this study, therefore completing accrual within 9 mo (if one stage) or 21 months (if both stages of the trial are completed).

### **14.2. Secondary Objectives**

#### **14.2.1. Safety and Tolerability**

Toxicity data (AEs, laboratory data and vital sign data) will be collected, tabulated according to CTCAE version 4.0 and summarized using descriptive statistics. Adverse events will be listed individually per patient. Safety and tolerability will be assessed after 6 patients are treated. A decision will be made, based on this, as to whether to proceed at the current dose/frequency schedule. Patients evaluable for this will have needed to have received at least 1 dose of the treatment regimen.

#### **14.2.2 Progression-Free Survival and Overall Survival**

Progression-free survival (PFS) and overall survival (OS) will be estimated using Kaplan Meier method. For PFS, patients will be followed up from the date of the first dose of the treatment regimen until disease progression (by RECIST) or death, whichever comes first. For OS, patients will be followed up from the date of the first dose of the treatment regimen until death. Patients who do not experience the event of interest during study time will be censored at the time of the last available follow-up. Median PFS/OS, as well as 1-year and 2-year PFS and OS will be reported, with the corresponding exact 95% confidence intervals.

#### **14.2.3 Correlative studies**

The association between BOR and molecular aberrations (*FGFR1* amplification status, *PIK3CA* mutations, *PTEN* mutations, PTEN loss, *DDR2* mutations) will be examined using Fisher's exact test. This analysis will be exploratory and hypothesis generating.

### **15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES**

#### **15.1 Research Participant Registration**

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

#### **15.2 Randomization**

There will be no randomization in this phase II study.

### **16.0 DATA MANAGEMENT ISSUES**

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure

database (Clinical Research Database CRDB). Source documentation will be available to support the computerized patient record. The principle investigator will maintain ultimate responsibility for the clinical trial.

### **16.1 Quality Assurance**

Weekly meetings will occur to monitor patient accrual and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow up will be monitored periodically throughout the study period and potential problem will be brought to the attention of the study team for discussion and action. Random sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times a year, and more frequently if indicated.

### **16.2 Data and Safety Monitoring**

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSKCC were established and are monitored by the Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://mskweb2.mskcc.org/irb/index.htm>

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

## **17.0 PROTECTION OF HUMAN SUBJECTS**

Prior to enrollment of each patient, the risks, benefits, and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities, side effects, and alternative, non-protocol treatment options. The patients will be reminded that

participation in this clinical trial is voluntary and the patient may withdraw consent at any time.

Risks: The standard front-line treatment for patients diagnosed with advanced squamous NSCLC (unresectable or metastatic disease) and an adequate performance status is chemotherapy with a platinum-based regimen. It is possible that non-platinum chemotherapy in the front-line setting is less effective than standard platinum-based chemotherapy.

Benefits: It is hoped that this regimen will allow delivery of a highly-active cytotoxic chemotherapy combination which will prove at least as effective as a platinum-based combination chemotherapy in a group of patients who might otherwise be unable to receive standard platinum-based therapies. This study uses albumin-bound paclitaxel, which does not require steroid-premedication and thus, circumvents many of the infusion difficulties associated with the standard solvent-based taxanes, paclitaxel and docetaxel. Patients who progress on this treatment can still receive standard, second line chemotherapy and or participate in an alternative clinical trial.

Consent process: Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent which must conform to MSKCC IRB guidelines.

Costs: Patients will be charged for physician visits, routine laboratory and radiologic studies required for monitoring their condition. Patients will not be billed for the study drug, albumin-bound paclitaxel. CLIA-certified mutation testing (i.e. fragment analysis, Sequenom or standard sequencing) will be billed to the patient/patient's insurance.

Alternatives: Alternative treatment options include standard chemotherapy, best supportive care, or participation in other investigational studies.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's names or any other personally identifying information will not be used in reports or publications resulting from this study. Qualified monitors from MSKCC, Celgene (the manufacturer of albumin-bound paclitaxel), and the FDA may review patient records as required.

Patient safety: Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24 hour urgent care facility for outpatients. The PI or co-PIs will also be available at all times to organize any necessary intervention.

Monitoring of data to ensure safety: this study is to be monitored by institutional IRB. This incorporates an independent data and safety monitoring committee established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually and summarized by severity and causality.

## **17.1 Privacy**

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

## **17.2 Serious Adverse Event (SAE) Reporting**

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to [saegrade5@mskcc.org](mailto:saegrade5@mskcc.org). All other reports should be sent to [saemskind@mskcc.org](mailto:saemskind@mskcc.org).

For all other trials: Reports that include a Grade 5 SAE should be sent to [saegrade5@mskcc.org](mailto:saegrade5@mskcc.org). All other reports should be sent to [sae@mskcc.org](mailto:sae@mskcc.org).

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number

- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

### **17.1 Procedure for Reporting Serious Adverse Events to Celgene**

Celgene is required to evaluate and expedite reporting of serious adverse events to worldwide regulatory authorities; therefore, the appropriate parties, as specified in this section, must be notified immediately (within 24 hours of awareness) regarding the occurrence of any serious adverse event.

The procedure for reporting serious adverse events, regardless of causal relationship, is as follows:

- The investigator must inform Celgene in writing using the CRDB SAE report form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day.
- The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report.
- A final report to document resolution of the SAE is required. The Celgene tracking number (AX-CL-NSCLC-PI-003548) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to

Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

### **Celgene Drug Safety Contact Information**

Celgene Corporation  
Global Drug Safety and Risk Management  
Connell Corporate Park  
300 Connell Dr. Suite 6000  
Berkeley Heights, NJ 07922  
Fax: (908) 673-9115  
E-mail: [drug\\_safety@celgene.com](mailto:drug_safety@celgene.com)

### **Pregnancies**

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on albumin bound paclitaxel and gemcitabine, or within 3 months of the subject's last dose of albumin bound paclitaxel and gemcitabine, are considered immediately reportable events. The study drugs are to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

### **Male Subjects**

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking albumin bound paclitaxel and gemcitabine should notify the Investigator,

and the pregnant female partner should be advised to call their healthcare provider immediately.

## **18.0 INFORMED CONSENT PROCEDURES**

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. Only those individuals designated on the protocol title page as consenting professionals may obtain informed consent. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form. The Research Authorization requires a separate set of signatures from the patient.

Three copies of the Informed Consent will be signed and dated by both patient (or his or her guardian) and physician. One copy will be returned to the patient, one copy will be placed in the patient's medical record, and the third will be stored in the research file.

## **19.0 REFERENCES**

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